REMARKS

Status of the claims

Claims 118-183 are presently pending in the application and stand rejected under 35 U.S.C. § 112, first paragraph (enablement) and 35 U.S.C. § 103(a). Attached hereto is a currently pending claim set.

IDS

Applicants note that they have not received initialed copies of the 1449s submitted with the IDS submitted on October 30, 2001. Enclosed herewith are copies of these 1449s for the Examiner's convenience.

35 U.S.C. § 112, first paragraph

All pending claims stand rejected as allegedly non-enabled for methods of using a zinc finger protein with two or more regulatory domains and for methods of delivering a zinc finger protein to a cell. (Office Action, paragraph 3). Applicants address each issue in turn.

Regulatory Domains

As stated previously, the specification provides, to one of skill in the art, adequate guidance for making and using zinc finger proteins comprising two or more regulatory domains. See, for example, page 7, lines 23-24; page 12, lines 24-25; and page 29, lines 1-10. Moreover, in light of the inventors' demonstration that zinc finger proteins comprising a single regulatory domain function to modulate gene expression, the Office Action has provided no reason why one of skill in the art would believe that zinc finger proteins comprising two or more regulatory domains would not similarly function to modulate gene expression. For these reasons, Applicants believe that this rejection is improper and should be withdrawn.

Furthermore, the functionality of zinc finger proteins comprising two or more regulatory domains, as taught in the specification, has been demonstrated, as documented in a declaration by Dr. Andreas Reik filed in parent U.S. Application Serial No. 09/229,037, copy attached hereto as Appendix A. The data presented in Dr. Reik's declaration show that, in line with the teaching of the specification, zinc finger proteins comprising two or more regulatory domains modulate gene expression in cells. Accordingly, Applicants submit that the rejection should be withdrawn.

Delivery of Polypeptides

In the pending case, the Office acknowledges that the claims are enabled for methods in which a polynucleotide encoding a ZFP is introduced. However, the Examiner maintains that the

specification does not enable methods in which a ZFP polypeptide is introduced and that Applicants have not provided convincing evidence that direct delivery of proteins to cells would modulate gene expression. (Office Action, paragraph 4). In other words, the Office appears to be requiring that data be submitted.

By requiring data, the Office has not applied the proper enablement standard. It is axiomatic that working examples are **never** required in order to show enablement. MPEP 2164.02. Rather, the test of enablement remains whether Applicants' specification (in view of information known in the art) teaches one of skill in the art how to make and use the invention as claimed.

For the reasons previously of record, Applicants again submit that the specification fully enables the claimed methods. Indeed, there is no question that Applicants have enabled methods of modulating gene expression in which a polynucleotide is administered, where the polynucleotide encodes a ZFP. By administering the polypeptide itself, Applicants simply eliminate the steps of ensuring the polynucleotide is expressed in the cell. Furthermore, methods of introducing polypeptides into cells are well-established and the Office has issued a variety of patents in this regard. (See, *e.g.*, U.S. Patent No. 6,475,490 and 6,413,942). Still further evidence regarding the ability to delivery functional transcriptional factor proteins to cells is found in Debs et al. (1990) J. Biol. Chem. 265:10189-10192 (previously made of record in this case and copy attached hereto as Exhibit B of Appendix B). Debs is directly relevant to the issue at hand, namely whether transcription factors can be delivered to a cell as proteins and whether these proteins function in the cell after delivery. It is **not** relevant whether Debs teaches that these transcription factors modulate of endogenous genes (which Applicants submit they were the first to demonstrate).

Dr. Carl Pabo's Rule 132 Declaration, copy attached hereto as Appendix B, supports Applicants' position regarding protein delivery in all respects. In this declaration, Dr. Pabo establishes that administering zinc finger proteins to cells would not require undue experimentation in view of the guidance of the specification and general knowledge available at the time of filing:

> 5. It is my opinion that, as a technical matter, a skilled worker could have readily practiced the methods of the pending claims in light of the specification, together with the common general knowledge, tools and methods available as of the effective filing date of January 1999. I base this opinion on the facts set forth below; however, I call attention to the fact that introducing proteins into cells would not have required undue experimentation and, once introduced into the cell, these proteins would have been expected to modulate expression of endogenous genes. In addition, in drawing my conclusions, I

> have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the direction present in the specification, the state of the field at the time the application was filed and the level of skill in the art. ...

Based on the teachings of the specification and the state of the art at the time of filing, Dr. Pabo confirms that it would have required little or no experimentation for one skilled in the art to identify protein delivery vehicles and evaluate these vehicles for their ability to deliver functional engineered zinc finger proteins to a cell. (See, Pabo Declaration, paragraphs 5-9).

In sum, Applicants have provided ample factual evidence which demonstrates that the specification enables the pending claims throughout their scope. When properly considered, the evidence and facts of record clearly establish that the claims are fully enabled by the specification.

35 U.S.C. § 103(a)

Claims 118, 122, 126-130, 133, 134, 137, 148, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171, 174, 177, 180 and 181 stand rejected as allegedly obvious over the combination of Liu '96 in view of Choo '96 and Liu '97. (Office Action, paragraph 9). In addition, claims 131, 132, 139, 140, 154, 155, 161, 162, 175, 176, 182 and 183 stand rejected as allegedly obvious over the aforementioned references in light of various secondary references. It is asserted by the Office that, at the time the presently claimed subject matter was invented, it would have been obvious to one of skill in the art to modify the naturally-occurring zinc finger protein of Liu '96 by modifying its sequence, using methods disclosed by Choo '96 and Liu '97 and to use the modified zinc finger protein in the methods as claimed. The Office Action further states that Choo '96 shows methods for making engineered zinc finger proteins that bind a desired sequence and regulation of endogenous genes by zinc finger proteins[1]; while Liu '97 shows methods for making engineered zinc finger proteins of high specificity and affinity that can increase or decrease expression of a targeted gene.

The law is well settled that obviousness cannot be established where the motivation to combine the cited references is not present. Further, motivation to combine is lacking when the state of the art at the time the invention in question was discovered pointed researchers in a different direction than that in which the inventors proceeded. In this regard, the Federal Circuit has repeatedly recognized that proceeding contrary to the accepted wisdom in the art is "strong evidence of unobviousness." See, *In re Hedges* 228 USPQ 685, 687 (Fed. Cir. 1986); *W.L.Gore*

[1] Applicants note that Choo does not actually demonstrate regulation of an endogenous cellular gene, as claimed (see below).

& Assocs. Inc. v. Garlock, Inc. 220 USPQ 303, 312 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Because the aforementioned references, as well as the art as a whole, taught away from modulating the expression of an endogenous gene with an engineered zinc finger protein, Applicants respectfully traverse the rejection. Indeed, even after Applicants' effective filing date (January, 1999) the art continued to teach away from the regulation of endogenous genes using engineered zinc finger proteins.

Turning to the cited references, Liu'96 discloses changes in cell growth, and modulation of TGF-β1 protein levels, after introduction of a nucleic acid encoding a single naturally occurring zinc finger protein (EGR-1) into cultured cells. As noted previously by Applicants, Liu does **not** teach contacting EGR-1 with a target site in a gene, nor does Liu '96 disclose modulation of transcription.[2] Applicants note that a reference "is relevant for **all** that it teaches those of ordinary skill in the art." *In re* Fritch 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992), emphasis added. *See* also *In re Wesslau* 147 USPQ 391, 393 (CCPA 1965), wherein it is stated:

> It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

Liu '96, although disclosing the existence of sequences which might serve as potential EGR-1 binding sites, clearly fails to teach binding of EGR-1 to any of those sites, thereby failing to disclose a zinc finger protein (let alone an engineered zinc finger protein) contacting a target site in a gene, as claimed. Furthermore, Liu '96 fails to suggest that the EGR-1 protein could be engineered to modify its binding specificity. Thus, besides failing to disclose or suggest the claimed subject matter, Liu '96 additionally fails to provide motivation to combine its disclosure with those of Choo '96 and/or Liu '97.

For its part, Choo '96 does not disclose regulation of an endogenous gene. Rather, Choo discloses regulation of a chromosomally integrated, non-endogenous cDNA comprising portions of two different genes. Had Choo desired to regulate an endogenous cellular gene, he would have selected an engineered zinc finger protein that bound to a target sequence in an endogenous cellular gene, rather than the zinc finger protein he did select, which binds to a breakpoint junction sequence in a cDNA. After selecting a zinc finger protein to bind to his non-

[2] See response dated April 17, 2002 noting that Liu '96 specifically states that they have not demonstrated binding of EGR-1 to a target site in a gene (see Liu '96 at page 11,835, second column, lines 23-26).

endogenous gene, Choo then had to transfect his non-endogenous fusion cDNA into cells and to select cells that had randomly integrated the non-endogenous cDNA into their chromosomes. Only after Choo had performed all of these manipulations could his ZFP be tested. The additional time and effort expended by Choo to construct, transfect and attempt to regulate his non-endogenous gene indicates that Choo **preferred** to regulate non-endogenous genes with his engineered zinc finger proteins, thereby teaching away from the presently-claimed methods. Because Choo '96, as a whole, teaches away from regulation of endogenous genes, he provides no motivation to combine his disclosure with that of Liu '96.[3]

Liu '97 (like Choo '96) discloses regulation of a non-endogenous extrachromosomal reporter gene. Although broad, general statements about potential applications of engineered zinc finger proteins to gene therapy are made, no teaching that would provide a reasonable expectation of success in either regulating an endogenous gene or associating the regulation of an endogenous gene is provided by Liu '97. Furthermore, and again like Choo '96, Liu '97's disclosure of the use of zinc finger proteins to regulate non-endogenous reporter genes provides no motivation to combine his disclosure with that of Liu '96.

Perhaps the most telling indictment of Liu '97 as a § 103 reference is the fact that subsequent papers from the **same** laboratory continued to teach the use of engineered zinc finger proteins for regulation of non-endogenous reporter genes, including a paper (Segal et al.) that was published two months after the priority date of the present application. (See, Beerli *et al.* (1998) *Proc. Natl. Acad. Sci. USA* **95**:14,628-14,633; Segal *et al.* (1999) *Proc. Natl. Acad. Sci. USA* **96**:2758-2763). Indeed, it was not until more than a year after the priority date of the present application that an example of regulation of an endogenous gene using an engineered zinc finger protein was published. (See, Beerli *et al.* (2000) *Proc. Natl. Acad. Sci. USA* **97**:1495-1500). In this publication, from the same laboratory as that of the Liu '97 reference, the authors stated:

> While our early experiments have focused on the regulation of genes transiently introduced into cells, **we realized that the willful and specific regulation of endogenous genes with designed transcription factors has remained an unmet challenge in biology**. Beerli et al (2000) *Proc. Natl. Acad. Sci. USA* **97**:1495-1500; emphasis added)

[3] Furthermore, as stated above, Liu '96 fails to teach regulation of transcription of an endogenous gene (as claimed), disclosing only effects on cell growth and protein levels; thereby providing even further disincentive to combine his disclosure with that of Choo.

Thus, the Liu '97 reference teaches away from the regulation of endogenous genes and the authors of this reference continued to teach away from endogenous gene regulation, in subsequent publications, for an additional three years, until over a year after the priority date of the present application.

To summarize, at the time of the filing of the priority application, the field of engineered zinc finger proteins was solely concerned with the regulation of non-endogenous genes, and the field continued to teach regulation of non-endogenous genes for over another year. There was no motivation in the art, as of the filing date, to regulate an endogenous gene with an engineered zinc finger protein and, hence, no motivation to combine disclosures of engineered zinc finger proteins with disclosures concerning naturally occurring zinc finger proteins. None of the secondary references used in the rejection of these claims cure the deficiencies of the primary references, as set forth above.

In light of the clear teachings in the art away from the regulation of endogenous genes with engineered zinc finger proteins, up to and beyond Applicants' priority date, Applicants believe that all of the pending claims are non-obvious, and request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Obviousness-Type Double Patenting

The Examiner again asserts that double patenting exists as between certain of the instant claims and those of copending applications 09/229,037; 09/478,681; and 09/897,844. (Office Action, paragraphs 15-18).

With regard to the latter two copending applications, Applicants request that the provisional double patenting rejections be held in abeyance until the claims in those applications proceed to allowance.

Turning to the provisional double-patenting rejections based on 09/229,037, Applicants again submit that because the pending application is a divisional of 09/229,037, the rejection is entirely improper.

It is axiomatic that claims directed to subject matter deemed by the Office to be separately patentable over claims in the same, originally-filed application **cannot** be subject to a an obviousness-type double patenting rejection based on the original application. Indeed, as stated in *In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998):

> [I]f the PTO determines that more than one distinct invention was claimed in a single application, 35 U.S.C. Section 121 authorizes the Commissioner to restrict the claims in the application to a single invention. *See,* Manual of Patent Examining Procedure, 6th ed., rev. 1, Section 806 ("MPEP") (where inventions are independent, restriction to one thereof is ordinarily proper;

> where inventions are related as disclosed but are distinct as claimed, restriction may be proper). If the claims are so restricted, one or more divisional applications can then be filed containing the claims that were the subject of restriction. When such a divisional application is filed, the PTO is prohibited from using the claims of the patent issuing on the application that prompted the restriction requirement as a reference against the claims of any divisional application. *See* 35 U.S.C. Section 121; *see also* MPEP Section 804.01. **Hence, by filing all of its related claims in one application, such an applicant is protected from an obviousness-type double patenting rejection** ... (emphasis added).

Here, the claims in 09/229,037 were subject to restriction as between methods of modulating gene expression by administering a protein and methods of modulating gene expression by administering a nucleic acid). See, Restriction Requirement mailed July 28, 1999. In support of the restriction requirement the Office stated:

> Inventions of Groups I and II are biologically and functionally distinct from each other and one does not render the other obvious. The methods of Groups I-II comprise steps which are not required for or present in the methods of the other group: administration of a protein to a cell in order to modulate expression of a cellular gene (Group I) and administration of a nucleic acid to a cell in order to modulate expression of a cellular gene (Group II). ... Therefore, the inventions of these different, distinct groups are capable of supporting separate patents. (Restriction Requirement in 09/229,037 dated 7/28/99, paragraph bridging pages 2-3).

Following Applicants traversal, the Restriction was made final:

> [Applicants' traversal] is not found persuasive because the administration of genetic material for inhibiting cellular expression is materially and functionally different than the administration of proteins for inhibiting cellular expression. Although genetic material that it administered for inhibiting gene expression may express a protein which in turn inhibits gene expression, this is materially and functionally different than directly administering a protein (i.e., even the same protein) for inhibition of gene expression. The requirement is still deemed proper and is therefore made FINAL. (Office Action in 09/229,037 dated 1/5/00, page 4).

Since the Office has repeatedly determined that the claims in the pending divisional are distinct from those issuing in the parent application, it is **prohibited** from basing an obviousness-type double patenting rejection on the claims in the parent application. Therefore, the double-patenting rejections based on 09/229,037 are improper and should be withdrawn.

CONCLUSION

Applicants believe that the claimed subject matter is fully enabled in light of the teachings of the specification, and that the accompanying declarations of Dr. Reik and Dr. Pabo attest to enablement of the application as filed. Applicants further believe that the present claims are non-obvious for the reasons presented above and in previous responses. If any issues remain to be addressed, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,
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